Group A, B, and D, 200 µg for Group C) and were monitored for 144 hours (Group A, B, and C) or 72 hours (Group D). PK samples were analyzed by liquid chromatography coupled to tandem mass spectrometry. PK parameters of selexipag and ACT-333679 were explored using ratios of geometric means and their 90% CIs.
Results: PK results (geometric mean (95% CI)) are presented in the **table** below:

	Group A		Group B		Group D	
Parameter	Selexipag	ACT-333679	Selexipag	ACT-333679	Selexipag	ACT-333679
Cmax1 [ng/mL]	3.9 (2.8–5.3)	4.5 (3.1–6.7)	5.4 (3.9–7.3)	5.3 (4.6–6.0)	1.9 (1.5–2.4)	3.8 (3.0–5.0)
tmax2 [h]	1.0 (1.0–4.0)	5.0 (3.0–6.0)	2.0 (1.0–6.0)	6.0 (4.0–7.0)	1.0 (1.0–2.0)	4.0 (4.0–6.0)
t1/23 [h]	1.6 (1.3–2.1)	6.5 (4.9–8.6)	2.2 (1.6–3.0)	15.9 (10.1–25.0)	1.1 (0.8–1.4)	12.6 (9.1–17.5)
AUC0-∞4 [ng*h/mL]	10.9 (8.6–13.8)	29.6 (20.6–42.6)	23.5 (17.0–32.4)	56.1 (42.8–73.5)	5.3 (4.5–6.2)	25.3 (21.9–29.3)

[1]peak concentration; [2]time to reach Cmax, median (range); [3]terminal half-life, [4]exposure from 0 to ∞.

The free fraction of both compounds in plasma increased only in Group B (30%). Group C PK data are not included here (2 subjects only). Selexipag 400 µg was generally well tolerated in all groups. Ten subjects reported 14 adverse events: 4, 6, 2, and 2 in Group A, B, C, and D, respectively. One serious adverse event (hepatic encephalopathy) occurred in Group C, in the context of urinary infection and previous history of encephalopathy. No clinically relevant changes in clinical laboratory variables and electrocardiograms were observed.
Conclusion: Selexipag exposure increased in subjects with mild or moderate liver impairment compared with healthy subjects whereas exposure to ACT-333679 remained unchanged in subjects with mild liver impairment and doubled in subjects with moderate liver impairment. No conclusion could be drawn for severe liver impairment.
Disclosure of Interest: None declared.

PP195—VORICONAZOLE ADJUSTMENT FROM TWICE TO THREE TIMES DAILY IN CYSTIC FIBROSIS LUNG TRANSPLANT PATIENTS

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Introduction: Azole antifungal drugs display a nonlinear pharmacokinetic profile and present pharmacokinetics/pharmacodynamic relationships that is the reason why therapeutic drug monitoring is highly recommended. In time, we observed that cystic fibrosis lung transplant patients show an extensive metabolism and that dose escalation, without reducing time between dose intervals, cannot lead to reach optimal blood level. The objective of this work is to evaluate the administration of voriconazole 3 times daily to reach the therapeutic range (1–4.5 mg/L) in this population.
Patients (or Materials) and Methods: A retrospective study was carried out on cystic fibrosis lung transplant patients. Inclusion criteria were as follow: intravenous administration of voriconazole twice daily with a trough concentration <0.5 mg/L, and then dose adjustment from twice to 3 times daily. Trough concentration was compared before and after dose adjustment. A validated high-pressure liquid-chromatography tandem mass spectrometry assay was used to determine voriconazole concentrations
Results: Seven cystic fibrosis patients have been included (4 males, 3 females)

	n	7
	age (years)	24.7 (5.44) [21–32]
	weight (kg)	48,8 ± 4,95 [44–56)]
	time posttransplant (days)	22,8 ± 27,13 [8.5–83.5]
	Before dose adjustment	After dose adjustment
Trough concentration (mg/L)	0.25 (0.15) [0.03–0.52]	2.26 (1.10) [0.68–4]
Voriconazole dose (mg/kg)	6,47±2,12 [4–9.2) × 2/d	7.35 (1.52) [5.36–9,17] ×3/d

After dose adjustment from twice to 3 times daily, trough concentrations for 6 patients were in the therapeutic range. Only 1 was under 1 mg/L.
Conclusion: In this population of patients, recommended twice daily dose of 6 mg/kg for the first 24 hours followed by 4 mg/kg cannot lead to trough concentration of 1 mg/L. This adjustment from twice daily to 3 times daily could be a good method to reach the therapeutic range. Nonetheless, more studies should be planed concerning efficacy and tolerance. These data illustrate also the nonlinear pharmacokinetic of voriconazole: from 6.5 mg/kg × 2 per day to 7.4 mg/kg × 3 per day, trough concentrations display a 10-fold increase.
Disclosure of Interest: None declared.

PP196—ENANTIOSELECTIVE METABOLISM OF VENLAFAXINE IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH PSORIASIS

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Introduction: Psoriasis is a common chronic inflammatory skin disease, which has long been recognized to be associated with depression, among other comorbidities. Venlafaxine (VLX), a racemic mixture of (S)-(+) and (R)-(-) enantiomers indicated for the treatment of depressive illness, is metabolized to O-desmethylvenlafaxine (ODV), N-desmethylvenlafaxine (NDV) and N,O-didesmethylvenlafaxine (NODV). Considering that inflammatory disease states have been associated with down-regulation of drug-metabolizing enzymes and transporters in the liver and considering that in psoriasis many CYP in skin are induced, the present study evaluates the influence of psoriasis on kinetic disposition and metabolism of venlafaxine enantiomers.
Patients (or Materials) and Methods: Patients with psoriasis (n = 12) and healthy volunteers (n = 11) were treated with a single oral dose of racemic venlafaxine (150 mg). Serial blood samples were collected up to 48 hours after drug administration. Venlafaxine and its metabolites enantiomers were analyzed in plasma samples by LC-MS/MS coupled with a chiral column Chirobiotic V. Pharmacokinetics parameters were evaluated using the WinNonlin software.
Results: Compared with healthy subjects who were similar overall in terms of age, sex, and body mass index (BMI), the means area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC0-∞) for venlafaxine and its metabolites enantiomers did not differ (unpaired *t* test) in patients with psoriasis. The following

$AUC_{0-\infty}$ values were obtained, respectively, for patients with psoriasis and healthy volunteers: (S)-(+)-VLX, 729.7 vs 647.9 ng·h/mL; (R)-(-)-VLX, 532.0 vs 327.6 ng·h/mL; (S)-(+)-ODV, 2742.7 vs 2463.1 ng·h/mL; (R)-(-)-ODV, 2977.0 vs 2603.6 ng·h/mL; (S)-(+)-NDV, 281.7 vs 60.8 ng·h/mL; (R)-(-)-NDV, 507.2 vs 192.3 ng·h/mL; (S)-(+)-DDV, 758.6 vs 585.5 ng·h/mL; and (R)-(-)-DDV, 563.5 vs 482.9 ng·h/mL.
Conclusion: Psoriasis did not alter the kinetic disposition and metabolism of venlafaxine enantiomers following a single oral administration of the racemic drug.
Disclosure of Interest: None declared.

PP197—THERAPEUTIC DRUG MONITORING OF VANCOMYCIN AND AMINOGLYCOSIDES IN AN INTENSIVE CARE UNIT, A RETROSPECTIVE STUDY

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Introduction: Critically ill patients may display altered pharmacokinetic parameters. Therapeutic drug monitoring (TDM) is essential to optimize the use of antibiotics in intensive care units. Many TDM assessments may be inappropriate as a result of improper interpretation or collection timing. We assessed the practice of TDM of vancomycin and aminoglycosides in an adult intensive care unit.
Patients (or Materials) and Methods: We performed a retrospective analysis of all vancomycin and aminoglycosides plasma level determinations performed between January 1, 2011, and December 31, 2011, in adult patients admitted in the intensive care unit of Geneva University Hospitals, Switzerland.
Results: A total of 845 antibiotic plasma levels were performed in 193 patients, among which 773 levels could be interpreted. The majority of TDM were related to vancomycin (87%), while aminoglycoside TDM were less frequent (13%). For intermittent vancomycin, the dosage was not changed in 27% of high through levels and 23% of low through levels. A dosage increase was observed in only 22% of low through levels. Moreover, about one half of the samples were drawn too early. For continuous vancomycin, dosage was not changed in 17% of high plasma levels and 33% of low levels. A dosage increase was observed in only 30% of low levels. About 60% of the samples were drawn too early. For aminoglycosides, the dosage was not changed in 20 to 30% of the cases when high through levels were measured. As for vancomycin, samples were frequently drawn too early.
Conclusion: Our results show that the practice of TDM of vancomycin and aminoglycosides could be improved. Too high or too low levels did not systematically result in dosage changes and samples were frequently drawn too early.
Disclosure of Interest: None declared.

PP198—PHARMACOKINETICS OF IMIPENEM IN THE TREATMENT OF NOSOCOMIAL PNEUMONIA: COMPARISON OF 0.5 HR AND 3 HR INFUSION

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Introduction: In critically ill patients with hospital-acquired pneumonia, pathophysiologic changes alter the pharmacokinetics of antibiotics. Imipenem exhibits primarily time-dependent killing. Its administration by prolonging the intermittent infusion may increase time with serum concentrations above the minimum inhibitory concentration of the suspected pathogens (t > MIC).
Patients (or Materials) and Methods: Inclusion criteria were hospital-acquired pneumonia, treatment by imipenem/cilastatin, and expected continuation of mechanic ventilation for at least 48 hours from the recruitment into the trial. Enrolled patients were randomly divided into either bolus group (to receive 1-g imipenem over 30 minutes every 8 hours) or extended group (0.5 g administered over 3 hours every 6 hours). Imipenem plasma concentrations were determined by reversed-phase HPLC during the second day of imipenem treatment. Pharmacokinetic data were determined using a 1-compartment model. The target pharmacokinetic/pharmacodynamic parameter, percentage of dosing interval in which plasma concentration of imipenem exceeded 4 times the minimum inhibitory concentration (%t > 4 × MIC), was assessed using individual concentration–time curves for MIC of 0.5, 1, and 2 mg/L. Kolmogorov-Smirnov test was used to confirm normal distribution of data, which were then tested by unpaired *t* test.
Results: Twenty-two patients entered this study. Patients in both groups were matched with regard to other demographic data, renal functions, and severity of illness. The parameter % t >4 × MIC was comparable in both groups for MIC of 0.5 mg/L, ranging from 74% to 100% in bolus group and from 55% to 100% in extended group. For MIC of 1 mg/L, the difference in both groups was not statistically significant, ranging from 59% to 100% in bolus group and from 31% to 100% in extended group. However, in the extended group, in 2 patients (20%) imipenem concentration in plasma did not remain above 4 × MIC for 40 % of the dosing interval. All patients in the bolus group achieved the PK/PD target for MIC of 2 mg/L. In the extended group, majority of the patients did not achieve this target. On the other hand, imipenem plasma concentration was above 4 × MIC of 2 mg/L for more than 90% of the dosing interval in 1 patient in extended group.
Conclusion: In artificially ventilated patients with hospital-acquired pneumonia, prolonged infusion of imipenem/cilastatin to 3 hours (with reduced total daily dose) does not lead to an improvement of the main tested PK/PD parameter - time upon the 4 times suspected pathogen's MIC.
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Disclosure of Interest: None declared.

PP199—INTRACELLULAR CONCENTRATION OF DARUNAVIR AS AN INDICATOR FOR THE CLINICAL EFFICACY IN HIV PATIENTS

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Introduction: Darunavir (DRV), a protease inhibitor, potently suppresses the replication of wild-type and drug-resistant HIV-1, but its clinical efficacy varies greatly among individuals. Recently, the importance of the concentrations of DRV in blood cells, the site of action for DRV, has been focused. In this study, we assessed the influence of plasma and intracellular concentration of DRV on its clinical efficacy. The factors acting for the intracellular concentration of DRV is also investigated.